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5-THIA-ω-SUBSTITUTED PHENYL-PROSTAGLANDIN E DERIVATIVES, PROCESS FOR PRODUCING THE SAME, AND DRUGS CONTAINING THE SAME AS THE ACTIVE INGREDIENT

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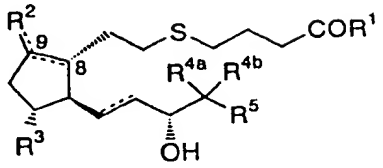


(1)

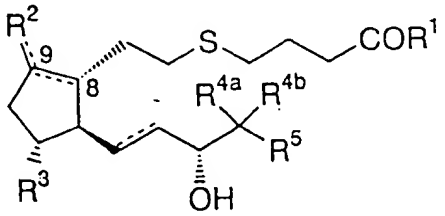
Abstract

5-Thia-ω-substituted phenyl-prostaglandin E derivatives represented by general formula (I) wherein each symbol is as defined in the specification. Because of being capable of bonding strongly to PEG_2receptors (in particular, the subtype EP_4), the compounds represented by general formula (I) are expected as useful in preventing and/or treating immunologic diseases, asthma, bone dysplasia, nerve cell death, lung failure, hepatopathy, acute hepatitis, nephritis, renal insufficiency, hypertension, myocardial ischemia, systemic inflammatory syndrome, ambustion pain, sepsis, hemophagous syndrome, macrophage activation syndrome, Still disease, Kawasaki disease, burn, systemic granulomatosis, ulcerative colitis, Crohn's disease, hypercytokinemia at dialysis, multiple organ failure, shock, etc. Moreover, these compounds participate in sleep disorders and platelet aggregation and, therefore, are expected as useful in preventing/treating these diseases.

Technical field

The present invention relates to 5-thia-ω-substituted phenyl-prostaglandin E derivatives.

More specifically, it relates to 5-thia-ω-substituted phenyl-prostaglandin E derivatives shown by general formula (I):



(I)

(wherein all of the symbols mean the same as discussed below).

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AE	United Arab Emirates
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GB	United Kingdom
GD	Grenada
GE	Georgia
GH	Ghana
GM	Gambia
GN	Guinea
GR	Greece
GW	Guinea-Bissau
HR	Croatia
HU	Hungary
ID	Indonesia
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IL	Israel
IS	Iceland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgyzstan
KP	Democratic People's Republic of Korea
KR	South Korea
KZ	Kazakhstan
LC	Saint Lucia
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LS	Lesotho
LT	Lithuania
LU	Luxembourg
LV	Latvia
MA	Morocco
MC	Monaco
MD	Republic of Moldavia
MG	Madagascar
MK	Macedonia (former Republic of Yugoslav)
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SL	Sierra Leone
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikstan
TM	Turkmenistan
TR	Turkey
TT	Trinidad and Tobago
TZ	Tanzania
UA	Ukraine
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US	United States of America
UZ	Uzbekistan
VN	Vietnam
YU	Yugoslavia
ZA	South Africa
ZW	Zimbab we

Background of the Technology

Prostaglandin E_2 (abbreviated as PGE_2) is known as a metabolite in the arachidonic acid cascade. It is known to protect cells, contract the uterus, induce pain, promote peristalsis of the digestive tract, have a stimulant effect, suppress gastric juice secretion, lower the blood pressure, and have a diuretic effect.

Recent research has demonstrated that there are subtypes of PGE_2 receptors, each of which has a different role. Four subtypes called EP_1, EP_2, EP_3, EP_4 are currently distinguished (Negishi, M. et al., J. Lipid Mediators Cell Signaling, 12, 379-391 (1995)).

As a result of research intended to discover compounds that specifically bind to each of these receptors, the present inventors attained the present invention by discovering that the compounds of the present invention bind specifically to EP_4.

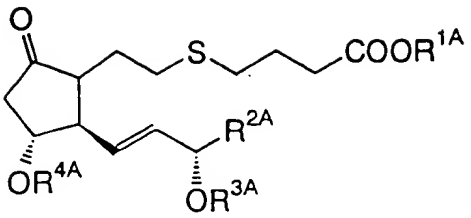
Since EP_4 receptors are believed to be associated with suppression of TNF-α production and potentiation of IL-10 production, the compounds of the present invention that bind strongly to EP_4 receptors are believed to be useful in the prevention and/or treatment of immunologic diseases (including autoimmune diseases such as amyotropic lateral sclerosis (ALS), multiple sclerosis, Sjogren's syndrome, chronic rheumatoid arthritis, and systemic erythematodes [sic] and post-organ transplant rejection response), asthma, bone dysplasia, nerve cell death, lung damage, hepatopathy, acute hepatitis, nephritis, renal insufficiency, hypertension, myocardial ischemia, systemic inflammatory reaction syndrome, burn pain, septicemia, hemophagocytosis, macrophage activation syndrome, Still's disease, Kawasaki syndrome, burns, systemic granulomatosis, ulcerative colitis, Crohn's disease, hypercytokinemia in dialysis, multiple organ failure, and shock. Since these receptors are also related to sleep disorders and platelet aggregation, these compounds are also useful in diseases that involve these.

The compounds of the present invention shown by general formula (I) can serve as drugs with few side effects because they bind weakly to the other subtypes and have no other effects.

On the other hand, compounds are known with position 5 of PG substituted by a sulfur atom and the ω-chain chemically modified. However, there has been no concrete disclosure of compounds with substituted or unsubstituted phenyl in the ω-chain.

For example, Japanese Kokai Patent Application No. Sho 58[1983]-198466 discloses the following 5-thia-prostaglandin derivatives that act to suppress platelet aggregation.

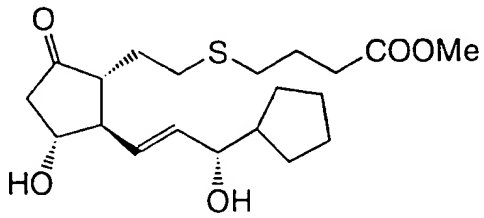
Specifically, the patent discloses that 5-thia-prostaglandins shown by general formula (A):



(A)

(wherein R^1 is a hydrogen atom or alkyl group having 1-10 carbon atoms, R^2 is a substituted or unsubstituted alkyl group having 1-10 carbon atoms or a substituted or unsubstituted cycloalkyl group having 5-6 carbon atoms, and R^3 and R^4 are the same or different hydrogen atoms or protecting groups) and nontoxic salts of acids when R^1 is a hydrogen atom are useful as antihypertensives and in the treatment and prevention of thrombosis because they suppress platelet aggregation and have a vasodilating effect.

The following ω-cyclopentyl compounds are disclosed in Application Example 3 as concrete compounds in this specification.



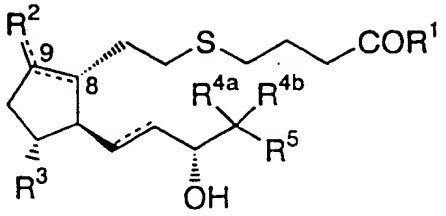
Disclosure of the invention

The present inventors conducted diligent research to discover stable compounds that bind specifically to EP_4 receptors and do not bind to other EP receptors or other prostanoid receptors.

As a result, they attained the present invention by discovering that this goal can be reached by introducing substituted phenyl groups into the ω-chain of 5-thia-prostaglandin.

As will be discussed below, compounds with sulfur atoms introduced at position 5 of the α-chain and phenyl groups substituted by specific functional groups introduced into the ω-chain were discovered to combine satisfactory stability with the property of strong binding activity to EP_4 and low binding activity to other prostanoid receptors, including other subtypes. The present invention was attained on the basis of this discovery.

The present invention relates to (1) 5-thia-ω-substituted phenyl-prostaglandin E derivatives shown by the general formula:



(I)

(wherein R^1 is a hydroxy, C_{1-6} alkyloxy, or NR^6R^7 group (wherein R^6 and R^7 are independently hydrogen or C_{1-4} alkyl),

R^2 is oxo, halogen, or O-COR^8 group (wherein R^8 is a C_{1-4} alkyl, phenyl, or phenyl (C_{1-4} alkyl)),

R^3 is hydrogen or hydroxy,

R^{4a} and R^{4b} are each independently hydrogen or C_{1-4} alkyl,

R^5 is a phenyl group substituted by the following groups:

i) 1-3 C_{1-4} alkyloxy-C_{1-4} alkyl, C_{2-4} alkenyloxy-C_{1-4} alkyl, C_{2-4} alkynyloxy-C_{1-4} alkyl, C_{3-7} cycloalkyloxy-C_{1-4} alkyl, C_{3-7} cycloalkyly-(C_{1-4} alkyloxy)-C_{1-4} alkyl, phenyloxy-C_{1-4} alkyl, phenyl-C_{1-4} alkyloxy-C_{1-4} alkyl, C_{1-4} alkylthio-C_{1-4} alkyl, C_{2-4} alkenylthio-C_{1-4} alkyl, C_{2-4} alkynylthio-C_{1-4} alkyl, C_{3-7} cycloalkylthio-C_{1-4} alkyl, C_{3-7} cycloalkyl (C_{1-4} alkylthio)-C_{1-4} alkyl, phenylthio-C_{1-4} alkyl, or phenyl-C_{1-4} alkylthio-C_{1-4} alkyl,

ii) C_{1-4} alkyloxy-C_{1-4} alkyl and C_{1-4} alkyl, C_{1-4} alkyloxy-C_{1-4} alkyl and C_{1-4} alkyloxy, C_{1-4} alkyloxy-C_{1-4} alkyl and hydroxy, C_{1-4} alkyloxy-C_{1-4} alkyl and halogen, C_{1-4} alkylthio-C_{1-4} alkyl and C_{1-4} alkyl, C_{1-4} alkylthio-C_{1-4} alkyl and C_{1-4} alkyloxy, C_{1-4} alkylthio-C_{1-4} alkyl and hydroxy, or C_{1-4} alkylthio-C_{1-4} alkyl and halogen,

iii) haloalkyl or hydroxy-C_{1-4} alkyl, or

iv) C_{1-4} alkyl and hydroxy, and

⋯ is a single bond or double bond; however, when R^2 is an O-COR^8 group, position 8-9 shows a double bond), nontoxic salts thereof, and cyclodextrin inclusion compounds thereof,

(2) a process for producing the same, and

(3) drugs that contain these as the active ingredient.

Detailed explanation of the invention

C_{1-4} alkyl shown by R^{4a}, R^{4b}, R^6, R^7, and R^8 in general formula (I) and by R^5 and R^8 means methyl, ethyl, propyl, butyl, and isomers thereof.

C_{1-6} alkyl shown by R^1 in general formula (I) means methyl, ethyl, propyl, butyl, pentyl, hexyl, and isomers thereof.

C_{2-4} alkenyl shown by R^5 in general formula (I) means vinyl, propenyl, butenyl, and isomers thereof.

C_{2-4} alkynyl shown by R^5 in general formula (I) means ethynyl, propynyl, butynyl, and isomers thereof.

C_{3-7} cycloalkyl shown by R^5 in general formula (I) means cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

Halogen shown by R^2 and by R^5 in general formula (I) means fluorine, chlorine, bromine, or iodine.

As is evident to persons skilled in the art, the symbol  means a single bond or a double bond, unless specifically stated otherwise,  represents bond coming out of the plane of the paper,  represents bonds extending behind the plane of the paper, and and  represent a mixture thereof or the possibility of either one or the other.

Unless specifically noted otherwise, the present invention encompasses all isomers. For example, the alkyl, alkenyl, alkynyl, and alkylene groups include linear and branched ones. Isomers (E, Z, cis, and trans) of the double bonds, rings, and condensed rings, isomers due to the presence of asymmetric carbon atoms (R and S compounds, α and β compounds, enantiomers, diastereomers), enantiomorphs with optical rotation (D, L, d, l compounds), polar compounds obtained by separation by chromatography (high and low polarity compounds), equilized [sic] compounds, compounds that are arbitrary proportions thereof [sic], and racemic mixtures are all included in the present invention.

The phenyl group substituents in R^5 in general formula (I) preferably occur at position 3, a combination of positions 3 and 4, or a combination of positions 3 and 5.

In the phenyl group, substituents in R^5 in general formula (I),

i) represent substitution by 1, 2, or 3 alkyloxyalkyl groups, etc.

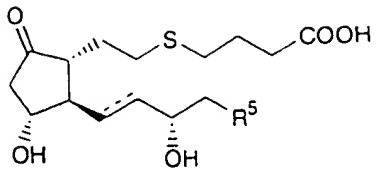
ii) represent substitution by a combination of at least one alkyloxyalkyl group, etc., and at least one alkyl group, alkyloxy group, hydroxyl group, or halogen atom,

iii) represents alkyl groups substituted by one or two halogen atoms or hydroxyl groups,

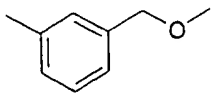
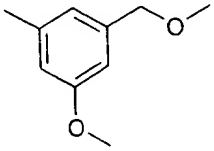
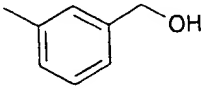
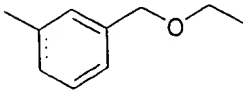
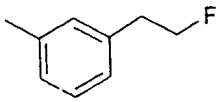
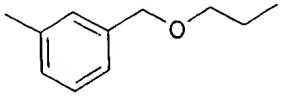
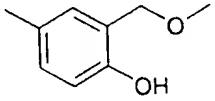
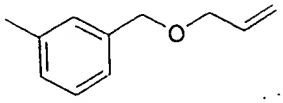
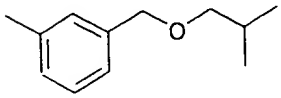
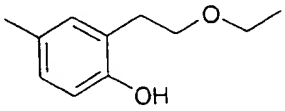
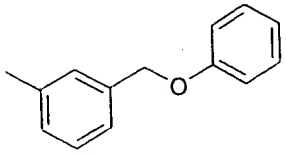
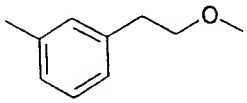
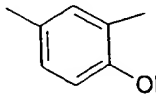
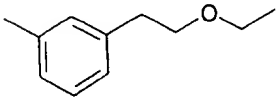
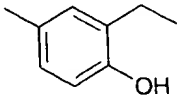
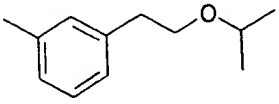
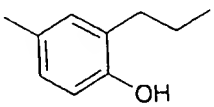
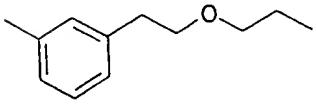
iv) represents substitution by a combination of at least one alkyl group and at least one hydroxyl group.

Preferred examples of the compounds of the present invention shown by general formula (I) include the compounds described in the application examples, the following compounds, and the corresponding esters and amides.

Table 1

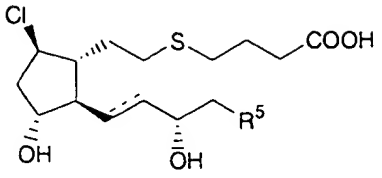


(1)

R^5



















R^5

Table 2



(2)

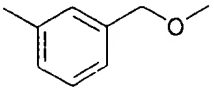
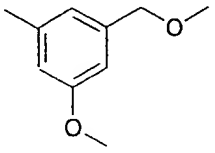
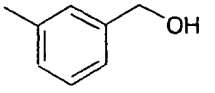
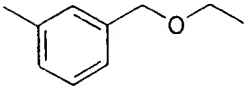
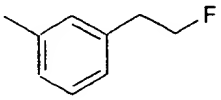
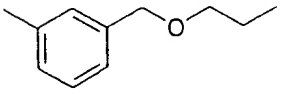
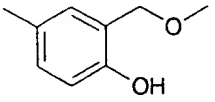
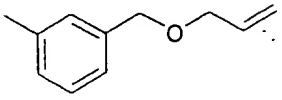
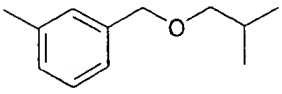
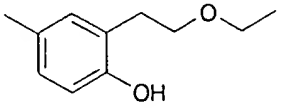
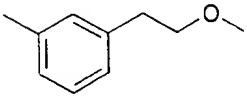
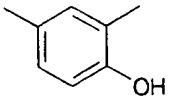
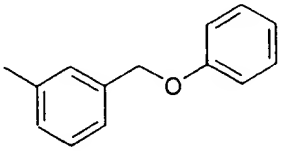
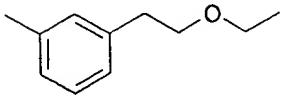
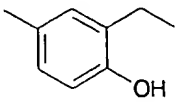
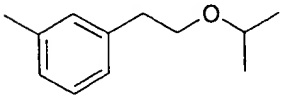
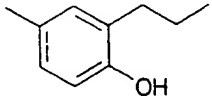
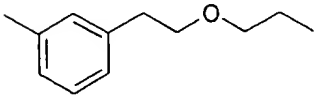
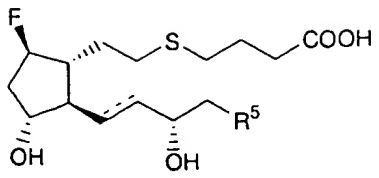
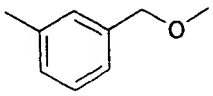
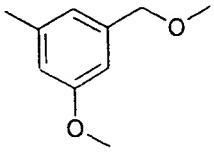
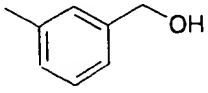
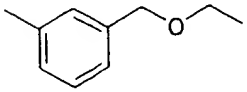
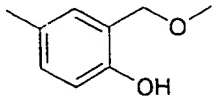
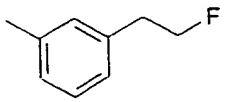
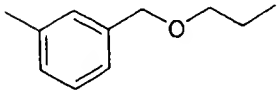
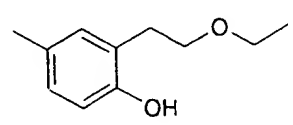
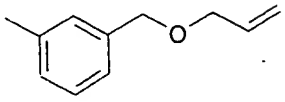
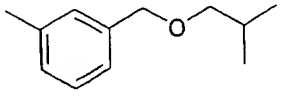
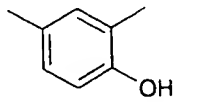
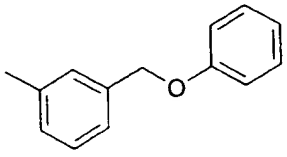
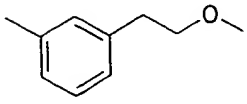
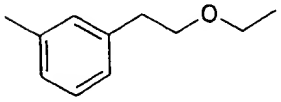
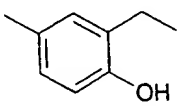
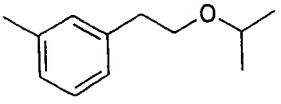
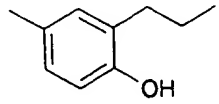
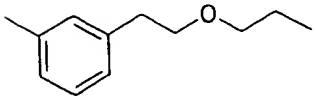
R^5



















Table 3



(3)

R^5		
		
		
		
		
		
		
		
		

Salts

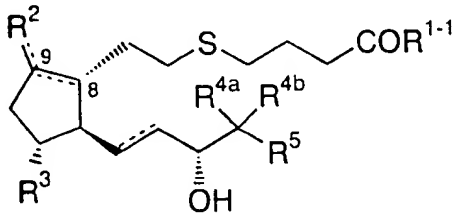
The compounds of the present invention shown by general formula (I) are converted to the corresponding salts by known methods. The salts are preferably nontoxic and water soluble. Examples of appropriate salts include salts of alkali metals (such as potassium and sodium), salts of alkaline-earth metals (such as calcium and magnesium), ammonium salts, and salts of pharmaceutically acceptable organic amines (such as tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)methylamine, lysine, arginine, and N-methyl-D-glucamine).

Cyclodextrin inclusion compounds

The compounds of the present invention shown by general formula (I) can be converted to cyclodextrin inclusion compounds by the methods described in Japanese Kokoku Patent Nos. Sho 50[1975]-3362, Sho 52[1977]-31404, or Sho 61[1986]-52146 using α-, β-, or γ-cyclodextrin or mixtures thereof. Conversion to cyclodextrin inclusion compounds is convenient when the compounds are used as drugs because it increases the stability and water solubility.

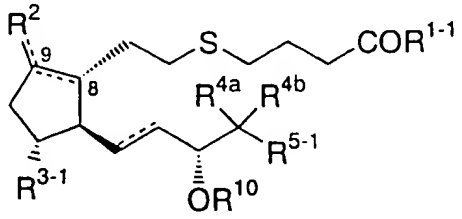
Process for the production of compounds of the present invention

(a) Compounds among those shown by general formula (I) wherein R^1 is C_{1-6} alkyloxy, i.e., compounds shown by general formula (Ia):



(Ia)

(wherein R^{1-1} is C_{1-6} alkyloxy and the other symbols mean the same as above), can be produced by a reaction to remove the protecting group from compounds shown by general formula (II):



(II)

(wherein R^{3-1} is a hydrogen atom or hydroxyl group protected by protecting groups that are removed under acidic conditions, R^{10} is a hydroxyl group protecting group that is removed under acidic conditions, R^{5-1} means the same as R^5 except that the hydroxyl groups among the groups represented by R^{5-1} are protected by protecting groups that are removed under acidic conditions, and the other symbols mean the same as above) under acidic conditions.

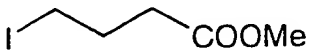
Examples of hydroxyl group protecting groups that are removed under acidic conditions include t-butyldimethylsilyl, triphenylmethyl, and tetrahydropyran-2-yl.

Hydrolysis under acidic conditions is a known technique, e.g., it is carried out at a temperature of 0-50°C using an inorganic acid (such as hydrochloric acid, phosphoric acid, hydrofluoric acid, or hydrogen fluoride-pyridine) or an organic acid (such as acetic acid, tosic acid, or trichloroacetic acid) in a water-miscible organic solvent (such as tetrahydrofuran, methanol, ethanol, dimethoxyethane, acetonitrile, or mixed solvents thereof).

* * *

Reference Example 17

Methyl 4-iodobutanoate



Sodium iodide (320 g) was added to an acetone (1100 mL) solution of methyl 4-chlorobutyrate (145.5 g) and refluxed while stirring for 11 h. After the reaction, the mixture was cooled to room temperature, filtered with Celite and the filtrate concentrated under reduced pressure. A mixture (500 mL + 500 mL) of ethyl acetate and water was added to the residue which was then extracted with ethyl acetate.

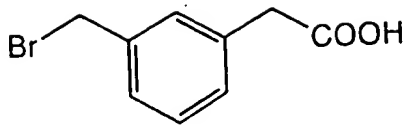
The organic layer was washed successively with aqueous saturated sodium thiosulfate solution (300 mL) and saturated saline, dried over anhydrous magnesium sulfate, and the solvent distilled off under reduced pressure to obtain the title compound (236.5 g).

TLC: Rf 0.36 (hexane:ethyl acetate = 9:1);

NMR (200 MHz, $CDCl_3$): δ 3.69 (s, 3H), 3.24 (t, J = 6.8 Hz, 2H), 2.46 (t, J = 7.0 Hz, 2H), 2.13 (tt, J = 7.0, 6.8 Hz, 2H).

Reference Example 18

3-Bromomethylphenylacetic acid



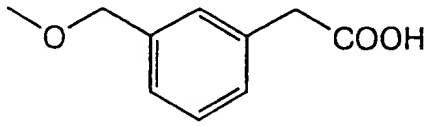
N-Bromosuccinimide (148 g) and 2,2'-azobisisobutyronitrile (AIBN; 1.37 g) were added to a carbon tetrachloride (1660 mL) solution of 3-methylphenylacetic acid (125 g) and heat refluxed. After the reaction had been completed, the solution was cooled by an ice bath. The white solids that precipitated were filtered with a glass filter and washed with carbon tetrachloride. The filtrate combined with the wash solution was concentrated and the residue obtained was dissolved in ethyl acetate. This was crystallized by adding hexane to obtain the title compound (59 g).

TLC: Rf 0.58 (hexane:ethyl acetate = 1:1 + 1% acetic acid);

NMR (200 MHz, $CDCL_3$): δ 7.36-7.18 (m, 4H), 4.48 (s, 2H), 3.66 (s, 3H).

Reference Example 19

3-Methoxymethylphenylacetic acid



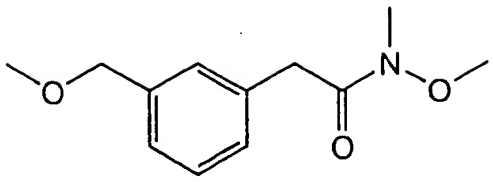
Methanol (800 mL) was added to sodium methoxide (160 g) while stirring in an argon atmosphere. A methanol (3200 mL) solution of 3-bromomethylphenylacetic acid (226 g, produced in Reference Example 18) was then added and refluxed for 20 min. After returning to room temperature, the methanol was distilled off and the residue was poured into 2N hydrochloric acid. Ethyl acetate was added to this solution. The organic layer was washed with saturated saline, dried over anhydrous magnesium sulfate, and concentrated to obtain the title compound (176.3 g).

TLC: Rf 0.58 (hexane:ethyl acetate = 1:1 + 1% acetic acid)

NMR (200 MHz, $CDCl_3$): δ 7.38-7.18 (m, 4H), 4.45 (s, 2H), 3.65 (s, 2H), 3.39 (s, 3H).

Reference Example 20

N-Methoxy-N-methyl-(3-methoxymethylphenyl)acetic acid amide



Methyl methoxyamine hydrochloride salt (289 g), 1-hydroxybenzotriazole (HOBt) monohydrate (166 g) and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide monohydrochloride salt (EDC; 284 mg) were added successively to a methylene chloride (2500 mL) solution of 3-methoxymethylphenylacetic acid (176.1 g, produced in Reference Example 19) in an argon atmosphere. N-Methylmorpholine (325 mL) was then added and stirred at room temperature.

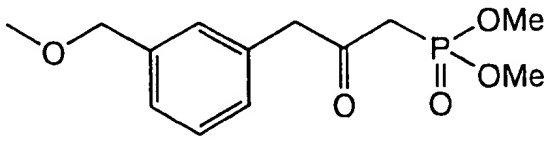
After 11 h, EDC monohydrochloride salt (94.7 g) and N-methylmorpholine (54.0 mL) were added and stirred for another 2 h. After filtering the reaction mixture, the solvent was distilled off under reduced pressure. Water (600 mL) and ethyl acetate (600 mL) were added and, after being completely dissolved, the mixture was poured into 2N hydrochloric acid (2000 mL). The hydrochloride salt was removed by filtering this mixture. The filtrate was separated and the organic layer was washed successively with 2N hydrochloric acid, water, aqueous saturated sodium bicarbonate solution, and saturated saline. The title compound (crude product, 200 g) was then obtained by concentration under reduced pressure.

TLC: Rf 0.58 (ethyl acetate);

NMR (200 MHz, $CDCl_3$): δ 7.36-7.18 (m, 4H), 4.44 (s, 2H), 3.78 (s, 2H), 3.61 (s, 3H), 3.38 (s, 3H), 3.20 (s, 3H).

Reference Example 21

Dimethyl 3-(3-methoxymethylphenyl)-2-oxopropylphosphonate



An anhydrous toluene (1500 mL) solution of dimethyl methylphosphonate (DMMP; 147 g) was cooled to -74°C in an argon atmosphere. n-Butyl lithium (714 mL; 1.52M hexane solution) was added to it over 1 h and stirred for 1 h. An anhydrous toluene (400 mL) solution of N-methoxy-N-methyl-(3-methoxymethylphenyl)acetic acid amide (200 g; produced in Reference Example 20) was then added over 30 min and stirred for another 2 h. Acetic acid (73.5 mL) was added to the reaction solution which was then warmed to room temperature. The reaction solution was poured into water and the organic layer was separated. The organic layer was

washed with water and saturated saline, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was refined by silica gel column chromatography to obtain the title compound (206.5 g).

TLC: Rf 0.22 (ethyl acetate);

NMR (200 MHz, $CDCl_3$): δ 7.38-7.11 (m, 4H), 4.45 (s, 2H), 3.90 (s, 2H), 3.82 (s, 3H), 3.77 (s, 3H), 3.40 (s, 3H), 3.11 (d, J = 23 Hz, 2H).

* * *